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**Section 6. PREGNANCY AND INFANT
HEALTH**

CONTENTS

Introduction

Evidence on the Effects of Smoking in Pregnancy

Health Effects of Lower “Tar” and Nicotine Cigarettes

Research Approaches

Recommendations for Human Studies

Recommendations for Behavioral Studies

Recommendations for Clinical Studies

General Studies

Placental Studies

Autopsy Studies

Breast-Feeding Studies

Recommendations for Physiologic-Pharmacologic Studies

Tobacco Smoke

Nicotine

Carbon Monoxide

Polycyclic Aromatic Hydrocarbons

Other Substances

Priorities for Research Recommendations

Summary

References

Introduction

Since Simpson (23) first reported that the newborn infants of women who smoked during gestation were of significantly lower weight than the infants of comparable nonsmokers, the adverse effects of maternal smoking on pregnancy have been increasingly appreciated. In 1979 the publication *Smoking and Health: A Report of the Surgeon General* (25) documented the considerable body of epidemiological, clinical, and laboratory evidence concerning the role of cigarette smoking in complications for the pregnant woman, fetus, newborn infant, and child. Although many of the effects on a pregnant woman and her child of smoking "regular" cigarettes manufactured during the past three or four decades are well known, possible differences between the effects of higher versus lower "tar" and nicotine cigarettes on the incidence and magnitude of these various complications are not known. The relative importance of "tar" and nicotine (commonly assayed in current cigarettes) versus the importance of carbon monoxide and several thousand other constituents of tobacco smoke (usually not measured) is not known. In fact, it is possible that compounds other than "tar" or nicotine are important in producing these effects. It is essential to elucidate these issues.

Evidence on the Effects of Smoking in Pregnancy

The complications of pregnancy ascribed to cigarette smoking may be divided into those that affect (1) the mother, (2) the embryo and fetus, (3) the placenta, and (4) the newborn infant and child. The mother, fetus, and placenta constitute an integrated organic unit rather than separate systems or organs. Thus, although separation of effects into these categories is convenient, it is also somewhat arbitrary. Some effects, such as spontaneous abortion and other reproductive loss, affect both the mother and fetus. Complications in different categories can occur concurrently. Cigarette smoking has been demonstrated to exert effects on each category.

Maternal complications of pregnancy that show a greater incidence among women who smoke cigarettes include placenta previa, abruptio placentae, vaginal bleeding during pregnancy, and, possibly, premature rupture of the membranes (13, 14). Lifetime smoking histories also affect the occurrence of placenta previa, abruptio placentae, and bleeding during pregnancy (17, 19). The incidence of amnionitis (infection of the amniotic fluid and its membranes) also is increased among women who smoke (16). The occurrence of the preceding complications appears to increase with the number of cigarettes smoked. For instance, the risk of placenta previa for mothers who smoke less than one pack per day is 25 percent greater than that of nonsmoking women, but is 92 percent greater in those who smoke one or more packs of cigarettes per day (14). Additionally, the risk of

abruptio placentae is increased 23 percent and 86 percent, respectively, in these two smoking-level groups compared with nonsmokers (14).

Virtually all of the more than 50 studies published, involving more than half a million births from many countries and ethnic groups, have been consistent in demonstrating that maternal smoking has an adverse effect on birthweight (25). These newborn infants weigh on the average 200 grams less than babies born to comparable women who do not smoke, and the decrement in birthweight varies with the number of cigarettes smoked (25). In an analysis of data from the Ontario (Canada) Perinatal Mortality Study, the number of newborns weighing less than 2,500 grams was 52 percent greater among women smoking less than one pack per day and 130 percent greater among women who smoked one pack or more per day, when compared with the pregnancies of nonsmoking women (12, 13). The contribution of this reduced birthweight to the occurrence of abruptio placentae or placenta previa is not clear (18).

Several studies have shown that the placental ratio (placental weight to fetal weight) is higher for the gestations of mothers who smoke (27). This increase in the placental ratio results from a decreased newborn birthweight and from a slight increase in absolute placental weight in heavier smokers (25). Preliminary results from the Columbia University study fail to show either smaller weight decreases in the newborns of mothers who smoke lower "tar" and nicotine cigarettes or a return to nonsmoker values in the placental to fetal weight ratios.

The risk of spontaneous abortion is 30 to 70 percent higher among pregnant smokers than among nonsmokers and increases with the number of cigarettes smoked (11). Rates of fetal deaths (occurring after 20 weeks of gestation) also increase significantly with the level of maternal smoking (3). The risk of premature delivery is 36 to 47 percent greater in mothers who smoke during pregnancy than in nonsmoking mothers; about 13 percent of all preterm births can be attributed to smoking (1, 3, 9, 13). This is an important factor in the increased risk of neonatal mortality among the infants of smoking mothers. Infants of women who smoke experience a mortality rate ranging from less than 10 percent to almost 100 percent greater than that among offspring of nonsmoking mothers. The excess risk of perinatal mortality varies, depending upon the number of cigarettes smoked and upon the presence of other high-risk factors (e.g., low socioeconomic group, a previous low-weight birth, or anemia) (15).

Several abnormalities of infancy and childhood occur more frequently among the offspring of mothers who smoke. Children of women who smoke during and after pregnancy experience higher rates of morbidity and mortality up to the age of 5 years. In Finland, smokers' children had more hospitalizations, more visits to the doctor, and more use of specialized services (20, 21). Significantly more infants of smoking parents are hospitalized for pneumonia and bronchitis (5, 6, 10). The

sudden infant death syndrome (SIDS) occurs more frequently among the children of parents who smoke (2, 24). Other long-term sequelae of maternal smoking during pregnancy are also of concern. Several studies suggest that older children of mothers who smoke have slight but measurable deficits in physical growth, intellectual ability, emotional development, and behavior (25). For instance, in Great Britain the physical growth of smokers' children remained less than that of nonsmokers' offspring, at least until age 11 (4). Associations have been reported between maternal smoking and deficits in neurological and intellectual development of the child. These include minimal cerebral dysfunction and abnormal or borderline electroencephalograms (8), hyperkinesia (7), and abnormal infant behavior patterns (22). These long-term effects of maternal smoking require attention because of their potential seriousness.

Thus, an excess risk of several disorders or death face the fetus and infant of the mother who smokes.

Although "tar," nicotine, carbon monoxide, and some other constituents of cigarette smoke have been shown to produce various effects, the specific etiologic agents and their mechanism(s) of action are not clearly established for these adverse effects on pregnancy.

Health Effects of Lower "Tar" and Nicotine Cigarettes

Although use of lower "tar" and nicotine cigarettes has grown markedly over the past decade, there are no data available that suggest that the developing fetus, the infant, or the pregnant woman are less harmed by cigarettes with lower levels of these constituents. There has been no demonstration of decreased risk of complications of pregnancy. There is no evidence of a decreased risk among smokers of spontaneous abortion or preterm birth, nor of an increase in the average weights of their babies. Newborn infants of smoking mothers continue to have a mean weight of 200 grams less than those of nonsmokers, a relation that is dose dependent. The risk of preterm delivery remains much greater for smoking mothers. Further, there is no evidence to date that maternal smoking of lower "tar" and nicotine cigarettes decreases the risk of perinatal mortality.

Most research reports to date have considered only the number of cigarettes smoked per day in quantitating smoke exposure, without adjusting for differences in yield of different cigarettes.

Research Approaches

Investigation into the effects of maternal cigarette smoking on pregnancy, the fetus, and the young child should include the following types of studies: (1) prospective epidemiologic studies comparing the course and outcome of pregnancy by maternal smoking habits; (2)

case-control studies of pregnancy complications including laboratory measurements of various body functions and constituents and a prospective study of pregnancy outcome; and (3) clinical and experimental research, often using laboratory animals, in which tobacco smoke or some of its constituents, commonly nicotine and carbon monoxide, are administered to the subject, animal, tissue, cell, or subcellular element, and the response quantified.

With numerous systems to be considered (the pregnant woman, the fetus, the newborn, the young child), and with various organs, tissues, cells, and subcellular elements potentially acted upon by a myriad of tobacco smoke constituents, the selection of appropriate study designs is a complex process. Further, the design of such studies is complicated by continuous changes in the composition of cigarettes over the past two decades. The spectrum of cigarette types, composition, and smoke yield varies enormously. In addition, the individual smoker's lifestyle, habits, and intake of other substances such as alcohol, caffeine, and drugs must be considered.

In view of the multiple variables involved, the recommendations that follow are those most likely to contribute significantly to an understanding of the character and magnitude of adverse effects of smoking cigarettes with varying levels of "tar" and nicotine on pregnancy. Research must define the relative importance of the several constituents, the impact of dose variations, and the mechanisms of action of the toxins in cigarette smoke.

Recommendations for Human Studies

Studies of populations of individuals with defined smoking histories have made an important contribution to elucidating the effects of smoking on various aspects of pregnancy, childbirth, and infant health. To date, no epidemiologic data exist to indicate lower risks of the aforementioned conditions in the pregnant mother, fetus, or infant resulting from the use of a lower "tar" and nicotine cigarette.

Present knowledge is sufficient that new, large prospective studies specifically designed to evaluate smoking effects are not necessary; rather, the approach should be, first, to encourage all prenatal care facilities to record smoking information, preferably with measurement of exhaled carbon monoxide. Second, the major source of information should be centers where continuing prospective evaluation of pregnancy is already being carried out in a systematic way, such as the Kaiser Permanente Cohort Study.

These centers should adopt a uniform practice of keeping detailed records of their patients' smoking habits, recording at each prenatal visit the number of cigarettes smoked, brands, filters, "tar" and nicotine content, and measured exhaled carbon monoxide (to estimate maternal and fetal COHb). Records of other exposures such as alcohol, coffee, and other drugs should also be kept. These and other relevant

personal, medical, and demographic factors should be analyzed or controlled in evaluating the outcome of these pregnancies (spontaneous abortions, later fetal deaths, complications of pregnancy, preterm deliveries, duration of gestation, birthweight, and neonatal and later conditions versus normal, live births).

These comprehensive, continuing studies are needed to elucidate the interrelationships of factors already known to affect pregnancy outcomes. It would be desirable to have several centers with large numbers of births follow a standard protocol for such studies.

Within the context of such a protocol, or possibly separate from it, case-control studies of spontaneous abortions, fetal death, preterm births, and particularly abruptio placentae, placenta previa, and premature rupture of membranes should be carried out. Patients who have not delivered at the time of ascertainment should be followed prospectively to delivery, together with their matched controls. Biochemical tests should be included in these studies to elucidate the mechanism of action of smoking in the increased incidence of these events. Any possible modification of these outcomes that accompany the use of lower "tar" and nicotine cigarettes should be examined.

A variety of other special clinical studies to test for differences in adverse pregnancy outcome by use of different cigarettes during pregnancy could be added to these larger monitoring operations or could be set up independently, using infants of matched smokers and nonsmokers. For example, (a) neonatal behavioral assessment (Brazelton scale), (b) auditory response testing of newborns, (c) neonatal and post-neonatal growth measurement, (d) special studies among very heavy smokers, and (e) placental studies could be performed.

Several epidemiologic studies now in progress might provide answers to some of these questions, for example, the study of spontaneous abortion at Columbia University in New York, or the Oakland Kaiser Permanente Cohort Study, which prospectively links smoking history and cigarette brand to all hospitalizations of approximately 50,000 women, many of childbearing age.

Studies have indicated that maternal smoking during pregnancy may be associated with impairment of physical and intellectual development, hyperkinesis, and changes in the infant's responsiveness (25, 26). The hypothesis that alterations in the constituents of cigarette smoke might affect the risk of these conditions needs to be tested. Differences in risk of long-term neurological consequences for a child exposed to maternal smoking should continue to be examined in existing data sets insofar as they contain appropriate information. Data files include (a) the Collaborative Perinatal Project (U.S.), (b) the 1958 and 1970 British Perinatal Studies (U.K.), (c) the Kaiser Permanente Cohort Study (Oakland), (d) the Finnish Perinatal Study (Finland), and possibly (e) the University of Washington Study (Seattle). Such studies must include consideration of possible confound-

ing factors such as socioeconomic status, nutritional status, alcohol use, and exposure to legal and illegal drugs.

In addition to studies documenting the maternal and fetal risks of varying levels of "tar," nicotine, and other constituents in cigarette smoke, there is need for study of the effect of cessation of smoking at different times in gestation on subsequent adverse events of pregnancy, including measures of birthweight, gestational age, perinatal mortality, and long-term sequelae. It will be important also to discriminate the effects of maternal smoking during gestation from those of parental smoking during infancy and childhood.

The combined effect of such studies would be to define any differences by cigarette "tar" or nicotine yield in the incidence of maternal complications or fetal or newborn sequelae, relative to both nonsmokers and smokers of different products.

Recommendations for Behavioral Studies

The factors and influences that lead an individual to start smoking and to maintain the habit despite knowledge that it poses health risks are complex. In view of the absence of evidence that lower "tar" and nicotine products pose less risk to pregnancy outcome, the description of smoking patterns among pregnant women and the investigation of motivational factors in this population are critical to the design of appropriate public health programs.

Some studies indicate that cessation of smoking early in gestation results in a pregnancy and fetus with risks of low birthweight similar to those among nonsmokers (25). Clinical studies could be conducted of pregnant women who refuse to quit smoking, in order to define the time intervals during which cessation of smoking results in a risk indistinguishable from those of nonsmokers. In view of the demonstrated effects of nicotine, carbon monoxide, and other tobacco constituents, rapid smoking techniques for cessation are contraindicated in pregnant women. Exhaled carbon monoxide should be measured at each visit, and the results used to explain to the mother that her baby's oxygen supply as well as her own is reduced by carbon monoxide from the cigarettes.

Further, considerable evidence indicates that the majority of women initiate smoking during their teens and pre-teens. Therefore, behavioral studies should focus on the prevention of initiation of smoking in this age group. Adolescents are a high risk group during pregnancy because of many factors, such as inadequate nutrition, anemia, inadequate prenatal care, and the use of illicit drugs. Adolescents who smoke during pregnancy constitute a particularly important group because of the coexistence of smoking and other risk factors. Intervention techniques must be found that effectively illustrate to the pregnant adolescent how smoking affects her body and fetus and that assist in cessation attempts. Such demonstrations might include

measurement of increases in fetal heart rate and decreases in fetal respiratory rate after smoking.

Studies of lifetime smoking experience should describe the role of pregnancy in changing smoking, such as cessation attempts and successes, brand choices, and number of cigarettes smoked daily. A logical extension of this study would define how the techniques of smoking cessation during the course of gestation may differ for pregnant women compared with those directed to smokers in general. The applications of such studies are particularly important for women who smoke heavily as well as for those women at high risk because of other factors.

Recommendations for Clinical Studies

General Studies

The adverse health consequences of cigarette smoking for the individual smoker extend beyond the pregnant smoker. As do the taking of drugs, exposure to workplace chemicals, or voluntary exposures to toxic substances such as alcohol, smoking by pregnant women affects the health of her fetus. The implications of this extended responsibility cannot be overstressed.

The effects of heavy smoking (two or more packs a day) on the pregnant woman, her fetus, and child have not been well defined. If adequate numbers of pregnant women who are very heavy smokers (two or more packs per day) could be identified, a special study should be undertaken to compare them with nonsmokers matched on important factors, e.g., time of registration, age, parity, and socioeconomic status. A prospective study should examine heavy smokers, including users of modified lower "tar" and nicotine cigarettes, as well as nonsmokers. For these heavy smokers as well as for light smokers, maternal blood levels of nicotine, catecholamines, carboxyhemoglobin, thiocyanate, cadmium, and other suspect compounds should be examined during pregnancy. Such a study should monitor several fetal variables including cardiac electrical activity, breathing and other body movements, cerebral electrical activity, and periodic measurements of head growth (biparietal diameter). Following birth, placentas would be examined for morphometric and/or pathologic abnormalities. Newborn infants should be completely examined, including measurement of lung volume and brain size and neonatal behavior assessment using the Brazelton scale. Children should undergo long-term followup for neurologic function (e.g., hearing and visual disorders). Alternatively, certain aspects of neurological dysfunction should be examined by case-control studies in which children with abnormalities are compared with normal neonates, matched by such factors as time of birth, gestational age, and socioeconomic status. Prenatal exposure to smoking by amount, type of cigarette, and yield and exposure to other

substances should then be compared to determine associations between neurological abnormalities and these exposures.

The mechanism(s) by which maternal smoking increases complications of pregnancy, such as spontaneous abortion, abruptio placentae, placenta previa, and premature rupture of the membranes are not clearly defined, despite the fact that these complications account for a significant portion of embryonic and fetal morbidity and mortality. Abruptio placenta will continue to result in anoxic fetal deaths. Preterm deliveries attributable to premature rupture of placental membranes will continue to pose the attendant hazard of neonatal death to the newborn infant.

Therefore, studies ought to test certain hypotheses about the mechanisms of action of cigarette smoke in these events. Instances of complications should be identified (i.e., placenta previa, abruptio placentae, premature rupture of the membranes, and probably spontaneous abortions). Controls should be selected for each case (matched by time of registration, gestational age at occurrence of complication, social status, age, parity, and perhaps other factors), and demographic factors and confounding exposure(s) to other compounds should be examined. A number of variables quantitating smoke exposure should be measured, including the concentrations of blood hemoglobin, carboxyhemoglobin, thiocyanate, copper, and various vitamins (A, B₁₂, C, and folate). The subjects should be followed to delivery, and the influence of measured factors related to outcome. Although at birth one could measure variables such as the biomechanical properties of membranes, tissue collagen concentrations, and cell number and size, such measures are not known to elucidate the mechanism of action of smoke constituents. Biopsies of the cervix from women with premature rupture of the membranes should be examined for concentrations of elastase or other enzymes that might play a role in premature dilation of the cervix. In instances of abruptio placentae and placenta previa (and in matched controls), that organ could be examined for morphometric or morphologic alterations.

Placental Studies

Placental morphology and morphometry are plagued by a lack of information and understanding of the relation of villous structure to the size (generation) of the associated blood vessels. Therefore, such morphometric studies of the placenta should be carried out in a laboratory dedicated to placental structure.

The ratio of placental weight to birthweight increases with numbers of cigarettes smoked daily. Light smokers' placentas may be slightly lighter and heavy smokers' placentas somewhat heavier than those of nonsmokers. The diameter to thickness ratio is also somewhat increased for smokers. Signs of "premature aging" are also seen in smokers' placentas, characterized by early appearance of calcium and

subchorionic fibrin (27). The described changes were somewhat smaller in magnitude than those described for high altitude or anemia. These studies did not, however, include consideration of the type of cigarette smoked. The factors that account for these changes and their mechanism of action are unknown.

Morphometric studies should be designed to determine what features of placental architecture are altered by maternal smoking and by the type of cigarette used. These studies would include examination of the trophoblast, blood vessels and their interrelations, relative maturation of the placenta including the presence of calcium and subchorionic fibrin, membrane thickness, relative size of the intervillous space, and evidence of pathologic alterations. In addition, other studies should examine ultrastructural features of the trophoblastic cells and blood vessels. Further studies should examine biopsies of the placental bed, including the decidua and endometrium of women who do and do not smoke.

Studies indicate that the blood of smoking women has lower concentrations of certain amino acids and vitamins A, B₁₂, C, and folic acid, among others, but the mechanism of these changes is unknown. Placentas from smokers of different cigarettes and matched controls should be studied for uptake kinetics and for intracellular to extracellular concentration ratios of amino acids and other compounds.

Autopsy Studies

The fetus of the mother who smokes weighs less than the fetus of a comparable nonsmoking mother, and this effect varies with the number of cigarettes smoked. However, the mechanism(s) whereby this change occurs is unknown. No evidence is available on how different cigarettes affect the occurrence of low birthweights. In an effort to determine whether decreased cell size, or cell number, or both, account for this change, we recommend that studies examine DNA concentrations (cell number) and DNA to protein ratios (cell size) in infants of smoking mothers suffering perinatal death.

One large study, corroborated by others, showed that, among perinatal deaths associated with maternal smoking, the largest categories of cause of death for stillborn infants were "unknown" causes or "hypoxia." The largest number of neonatal deaths were ascribed to "prematurity" alone. In an effort to elucidate specific causes and possible mechanisms of these deaths and the implications for newer cigarettes, dead fetuses and infants who die near the time of delivery, of smoking and nonsmoking mothers, should be subjected to thorough and careful autopsy by an experienced neonatal pathologist. Such studies may help elucidate differences in the smoker's infant who dies.

Fetal lung weight is decreased preferentially in animals exposed prenatally to carbon monoxide. Infants of smoking mothers experience increased risk of respiratory infections and pulmonary disease, and the

lungs may be altered in infants of smoking mothers who expire in the "sudden infant death" syndrome. In an effort to determine the morphologic basis and possible mechanism of these changes, the lungs of stillborns, or of newborn infants who expire, should be examined for morphologic and pathologic changes related to the smoking status of the mother. Some specific indices to be examined include alveolar type II cells, macrophages, and microcirculatory vascularization.

Fetal brain weight is increased (probably from edema) in animals exposed prenatally to carbon monoxide. The infants of smoking mothers experience increased risk of "minimal brain damage," hyperkinesia, and other neurologic disorders. In order to determine the morphologic basis and possible mechanisms of these changes, the brains of the dead fetuses or infants of this group should be examined for morphologic and pathologic changes. Some specific indices to be examined include neuronal and dendritic number and architecture. It may be of special importance to examine the brainstem because of altered respiratory control mechanisms.

Breast-Feeding Studies

Several products of tobacco smoke such as nicotine, cotinine, and thiocyanate are known to be secreted in breast milk. However, little is known about the dose-response relationship of smoking to the concentrations of these compounds. Breast milk of lactating mothers and the blood of their newborns should be examined for concentrations of nicotine, cotinine, thiocyanate, cadmium, and other toxins. In addition, breast milk from smoking mothers should be analyzed for the concentrations of leukocytes, monocytes, immune globulins, and other immunologically important factors, in addition to protein, fat, carbohydrate, and other constituents that affect newborn growth. Again, dose-response relationships should be explored.

Finally, breast-fed infants of smoking mothers should be examined for evidence of nicotine addiction and withdrawal symptoms (irritability, nervousness) at the time of weaning.

Some studies have indicated that maternal smoking suppresses lactation. Milk production and ability to nurse should be studied in smoking and nonsmoking women who want to breast feed their babies, including evaluation of the effects of stopping smoking and the use of lower "tar" and nicotine cigarettes.

Recommendations for Physiologic-Pharmacologic Studies

Laboratory studies in experimental animals have proved useful to test various hypotheses regarding the specific effects of the individual constituents of tobacco smoke, as well as mechanism(s) of action. Such laboratory studies should be carried out in a well-organized and careful

manner, and should consider exposure to tobacco smoke *per se* as well as to its individual constituents.

Tobacco Smoke

The introduction of modified, lower "tar" and nicotine cigarettes raises several questions regarding the effects of these tobacco products on the pregnant woman, fetus, and infant. Although purportedly lower in their yield of "tar" and nicotine, these cigarettes may still deliver a threshold level or more of carbon monoxide or other toxic products. Additionally, smokers may use certain techniques to increase the yield so that the delivery of "tar," nicotine, carbon monoxide, or other constituents is similar to, or perhaps in excess of, that of regular cigarettes.

Further, the possibility exists that there is a systematic difference in the style of smoking depending on "tar" or nicotine level. If smokers of lower "tar" and nicotine products uniformly take more puffs, larger puffs, or inhale more deeply, the actual dose of constituents experienced by the smoker would not be as low as that predicted by machine measurement. In addition, while the relative amounts of smoke absorbed may vary, differences in smoking pattern might also affect the relative proportions of constituents in the smoke inhaled, a fact that might well influence the probability of developing smoking-related health problems. Measurements of smoke constituents and breakdown products in the smokers' exhalations, serum, and other body fluids may provide better estimates of cigarette yield than smoking-machine results. Levels also differ by sex and during pregnancy.

Studies of the effect of tobacco smoke in animals present problems as to the dose of smoke actually received by the animal, the specific compound(s) responsible for the changes observed, and the concentration of these substances in blood or tissue. All such studies should include measurements of blood concentrations of nicotine, carboxy-hemoglobin, and perhaps other compounds, as well as tissue concentrations where appropriate.

Numerous animals have been used for studies on the effects of smoking. Ideally such studies should be carried out in subhuman primates, such as baboons trained to smoke. However, the technical difficulties and expense of such studies make this approach unrealistic. Consideration must be given to whether there is, in fact, a particular animal model that is optimal from the standpoint of relevance to human studies, availability, and expense.

As noted previously, an almost universal phenomenon is the decrease in birthweight of infants of smoking mothers. Animal studies must explore which components of cigarette smoke are most important in reducing the rate of fetal growth. Such studies should determine whether it is the rate of mitosis or cell number that is reduced, and

whether the smoking-associated reduction of fetal growth rate is caused by retarded growth of only certain organs or tissues.

Following birth, many children of smoking parents are continuously exposed to tobacco smoke. This may be a factor in the higher incidence of sudden infant death syndrome, hyperkinesis, "minimal brain dysfunction," and respiratory disorders in such children. Animal studies should be performed to examine the effects of passive smoking on newborn or young animals.

Nicotine

Nicotine is an important pharmacologic agent in tobacco smoke. Studies suggest that some smokers titrate their nicotine dose by altering the number of cigarettes smoked, the depth of inhalation, or the degree of occlusion of pores (in the case of low "tar" and nicotine cigarettes). The following major areas of inquiry should be studied:

1. Definition of the role of nicotine exposure during fetal life in birthweight reduction, behavioral development, and childhood growth retardation
2. Examination of the effect of nicotine on individual organ growth, including the fetal brain, adrenal glands, lungs, heart, and kidneys
3. Study of nicotine's contribution to neurologic disorders in children
4. Elucidation of the role of nicotine or its metabolites in carcinogenesis, alone or in combination with benzo[a]pyrene and other carcinogens in smoke
5. Definition of the effect of nicotine on human fetal blood catecholamine concentrations

Carbon Monoxide

Carbon monoxide, a product of incomplete combustion of carbonaceous compounds, is present in tobacco smoke in relatively high concentrations (1 to 6 percent). Hemoglobin avidly binds carbon monoxide as carboxyhemoglobin, decreasing the oxygen transport capacity of blood. Because of the relatively higher affinity of fetal hemoglobin for O₂ and CO, as compared with adult hemoglobin, a given carbon monoxide partial pressure results in a fetal blood carboxyhemoglobin level 10 percent greater than that of the smoking mother, while fetal arterial oxygen tension is only 20 to 30 percent that of the mother. Thus, the fetus experiences higher carboxyhemoglobin levels and a greater carbon monoxide-induced hypoxia than that occurring simultaneously in the mother. Exploration of the following questions should be undertaken:

1. Definition of the major physiological consequences of carbon monoxide exposure on the developing fetus or newborn
2. Elucidation of the dose-response relationship of carbon monoxide in disease occurrence

3. Examination of fetal adaptation to low carbon monoxide concentrations, and the mechanisms of any such adaptation
4. Definition of the patterns of growth, development, and maturation of the central nervous system and other organ systems exposed to chronic low-level carbon monoxide
5. Study of the periods during gestation when the fetus is particularly vulnerable to carbon monoxide

Polycyclic Aromatic Hydrocarbons

Benzo[a]pyrene (BaP) and other polycyclic aromatic hydrocarbons (PAH) are potent carcinogens. Little is known about the transplacental effects of these substances on the developing fetus. Examination of the following questions is needed:

1. Definition of the transplacental passage of BaP and PAH
2. Description of BaP or PAH distribution in the fetal organs and tissues
3. Examination of a possible role of BaP or PAH from maternal smoking in the growth and development of the fetal brain and other organs

It should also be noted that BaP and PAH are known inducers of the cytochrome oxidase (P₄₅₀) system, including aryl hydrocarbon hydroxylase (AHH). Such enzymes are involved in drug and steroid metabolism, among other functions. Thus, the PAH should be investigated for possible metabolic effects beyond those of carcinogenesis.

Other Substances

Numerous possibly toxic substances are present in cigarette smoke, including cyanide and cadmium. Little is known about the role of these compounds in altering fetal growth and development. Studies should examine the effects and mechanism(s) of action of these substances.

Priorities for Research Recommendations

The preceding discussion has presented many research issues that are major and valid questions. The primary emphasis, however, must be placed upon studies that determine the character and magnitude of the health hazards posed to the individual pregnant smoker and her offspring by the modified lower "tar" and nicotine cigarettes. Research to define the specific etiologic agents and their mechanism(s) of action must take a priority second to that of defining the risks.

It is through epidemiologic research that the answers to the most important questions will be reached. It is apparent that there is a need for refining the measurement of cigarette dosage and the quantitation of cigarette smoke exposure. A more accurate description of dosage must be an intrinsic part of epidemiologic research efforts that deal with smoking exposures. All obstetricians and prenatal clinics should

be strongly urged to record details of their patients' smoking habits at each visit.

Simultaneously, however, laboratory investigation should proceed in parallel to examine the specific compounds involved and their mechanisms of action. Research has contributed some knowledge of tissue, cellular, and subcellular effects. Further studies at these levels hold the promise of elucidating the mechanisms whereby these changes occur. Such studies may lead to a greater understanding of specific cigarette hazards by dosage and thereby suggest directions for epidemiologic studies. Conversely, epidemiologic data will suggest directions and specific questions for laboratory or clinical research. These approaches should proceed in concert for maximal results in understanding the problems of lower "tar" and nicotine cigarettes in the medical, biological, and social environments.

Summary

1. Cigarette smoking during pregnancy has been shown to have adverse effects on the mother, the fetus, the placenta, the newborn infant, and the child in later years. There is no evidence available that lower "tar" and nicotine cigarettes decrease or increase these health risks, relative to those posed by higher "tar" and nicotine cigarettes.
2. Problems that have been linked to smoking during pregnancy include placenta previa, abruptio placentae, vaginal bleeding, and reduced average birthweight of newborn infants.
3. Smoking by pregnant women increases the risk of spontaneous abortion, premature delivery, fetal death, and perinatal death. Parental smoking is associated with the sudden infant death syndrome.
4. The fetuses of smoking mothers have higher blood carboxyhemoglobin levels and lower fetal arterial oxygen levels than do the mothers.
5. Children of smoking mothers appear to show a greater susceptibility to some adverse health effects, such as bronchitis, pneumonia, and respiratory disease, during early childhood. Slight differences in physical growth and other forms of behavioral and intellectual development may be found in children as old as 11 years of age.
6. Although "tar," nicotine, carbon monoxide, and some other constituents of cigarette smoke produce deleterious effects, the specific etiologic agents and their mechanisms of action for adverse effects on pregnancy are not clearly determined. Thus, the relative importance of "tar" and nicotine, or carbon monoxide and other constituents of tobacco smoke in the etiology of adverse gestational and fetal events is not known.

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Section 7. BEHAVIORAL ASPECTS

CONTENTS

Research Priorities

- Controlled Studies To Determine the Role of Nicotine as a Primary Reinforcer in Cigarette Smoking
 - Animal Models of Nicotine Use
 - The Self-Administration of Nicotine by Animals
 - The Study of Tolerance and Physical Dependence
 - Nicotine Research With Humans
 - Compensatory Behavior in Smoking
 - Voluntary Switching
 - Controlled Switching
 - Additional Comments
 - Natural History of Smoking Along Both Biological and Psychosocial Dimensions
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Recommendations

- Clinical Testing Facilities and Standardized Research Cigarettes
 - Clinical Testing Facilities
 - Research Cigarettes
 - Machine-Smoked Yields of Lower "Tar" and Nicotine Cigarettes
 - Toxicology of Nicotine
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Summary

References